

# On the Complexity of Protein Local Structure Alignment Under the Discrete Fréchet Distance

Binhai Zhu <sup>\*</sup>

## Abstract

Protein structure alignment is a fundamental problem in computational and structural biology. While there has been lots of experimental/heuristic methods and empirical results, very little is known regarding the algorithmic/complexity aspects of the problem, especially on protein local structure alignment. A well-known measure to characterize the similarity of two polygonal chains is the famous Fréchet distance and with the application of protein-related research, a related discrete Fréchet distance has been used recently. In this paper, following the recent work of Jiang, *et al.* we investigate the protein local structural alignment problem using bounded discrete Fréchet distance. Given  $m$  proteins (or protein backbones, which are 3D polygonal chains), each of length  $O(n)$ , our main results are summarized as follows.

- If the number of proteins,  $m$ , is not part of the input, then the problem is NP-complete; moreover, under bounded discrete Fréchet distance it is NP-hard to approximate the maximum size common local structure within a factor of  $n^{1-\epsilon}$ . These results hold both when all the proteins are static or when translation/rotation are allowed.
- If the number of proteins,  $m$ , is a constant, then there is a polynomial time solution for the problem.

**Keywords:** Protein structure alignment, Fréchet distance, Discrete Fréchet distance, Approximation, NP-hardness

---

<sup>\*</sup>Department of Computer Science, Montana State University, Bozeman, MT 59717-3880, USA. Email: bhz@cs.montana.edu.

# 1 Introduction

As a famous distance measure in the field of abstract spaces, Fréchet distance was first defined by Maurice Fréchet a century ago [7]. Alt and Godau first used it in measuring the similarity of polygonal chains in 1992 [1]. It is well known that the Fréchet distance between two two-dimensional (2D) polygonal chains (polylines) can be computed in polynomial time [1, 2], and even under translation or rotation (though the running time is much higher) [3]. In three-dimensional space (3D), Wenk showed that given two chains with sum of length  $N$ , the minimum Fréchet distance between them can be computed in  $O(N^{3f+2} \log N)$  time, where  $f$  is the degree of freedom for moving the chains [22]. So with translation alone this minimum Fréchet distance can be computed in  $O(N^{11} \log N)$  time, and when both translation and rotation are allowed the corresponding minimum Fréchet distance can be computed in  $O(N^{20} \log N)$  time. These results can be generalized to any fixed dimensions [22]. While computing (approximating) Fréchet distance for surfaces is in general NP-hard [8, 12], it is polynomially solvable for restricted surfaces [4].

In 1994, Eiter and Mannila defined the *discrete Fréchet distance* between two polygonal chains  $A$  and  $B$  (in any fixed dimensions) and it turns out that this simplified distance is always realized by two vertices in  $A$  and  $B$  [6]. They also showed that with dynamic programming the discrete Fréchet distance between them can be computed in  $O(|A||B|)$  time.

Recently, Jiang, Xu and Zhu applied the discrete Fréchet distance in (globally) aligning the backbones of proteins (which is called the *protein structure-structure alignment* or more generally, the *protein global alignment* problem) [14]. In fact, in this application the discrete Fréchet distance makes more sense as the backbone of a protein is simply a polygonal chain in 3D, with each vertex being the alpha-carbon atom of a residue. So if the (continuous) Fréchet distance is realized by an alpha-carbon atom and some other point which does not represent an atom, it is not meaningful biologically. Jiang, *et al.* showed that given two 2D (or 3D) polygonal chains the minimum discrete Fréchet distance between them, under both translation and rotation, can be computed in polynomial time. They also applied some ideas therein to design an efficient heuristic for the original protein structure-structure alignment problem in 3D and the empirical results showed that their alignment is more accurate compared with previously known solutions.

In essence, the result of Jiang, Xu and Zhu [14] implies that the protein global alignment problem, which is to find all proteins in a given set  $\mathcal{P}$  similar to a query protein or some protein in  $\mathcal{P}$  (under translation and rotation), is polynomially solvable. However, very little algorithmic/complexity results is known regarding the protein local structure alignment problem. The only such recent result was due to Qian, *et al.* who showed that under the RMSD distance the problem is NP-complete but admits a PTAS [19]. On the other hand, there have been lots of experimental/heuristic methods with practical systems since 1989, e.g., SSAP [21], DALI [11, 10], CATH [17], CE [20], SCOP [5], MAMMOTH [18] and TALI [16]. In this paper, we show that if

many proteins are given then the local structure alignment problem, under the discrete Fréchet distance, is very hard; on the other hand, if only a small number of proteins are given then there is a polynomial time solution for the problem.

The paper is organized as follows. In Section 2, we introduce some basic definitions regarding Fréchet distance and review some known results. In Section 3, we show the hardness result for the protein local structure alignment problem. In Section 4, we show how to solve the problem when  $m$  is a constant. In Section 5, we conclude the paper with several open problems.

## 2 Preliminaries

Given two 3D polygonal chains  $A, B$  with  $|A| = k$  and  $|B| = l$  vertices respectively, we aim at measuring the similarity of  $A$  and  $B$  (possibly under translation and rotation) such that their distance is minimized under certain measure. Among the various distance measures, the Hausdorff distance is known to be better suited for matching two point sets than for matching two polygonal chains; the (continuous) Fréchet distance is a superior measure for matching two polygonal chains, but it is not quite easy to compute [1].

Let  $X$  be the Euclidean space  $\mathbb{R}^3$ ; let  $d(a, b)$  denote the Euclidean distance between two points  $a, b \in X$ . The (continuous) Fréchet distance between two parametric curves  $f : [0, 1] \rightarrow X$  and  $g : [0, 1] \rightarrow X$  is

$$\delta_{\mathcal{F}}(f, g) = \inf_{\alpha, \beta} \max_{s \in [0, 1]} d(f(\alpha(s)), g(\beta(s))),$$

where  $\alpha$  and  $\beta$  range over all continuous non-decreasing real functions with  $\alpha(0) = \beta(0) = 0$  and  $\alpha(1) = \beta(1) = 1$ <sup>1</sup>.

Imagine that a person and a dog walk along two different paths while connected by a leash; moreover, they always move forward, possibly at different paces. Intuitively, the minimum possible length of the leash is the Fréchet distance between the two paths. To compute the Fréchet distance between two polygonal curves  $A$  and  $B$  (in the Euclidean plane) of  $|A|$  and  $|B|$  vertices, respectively, Alt and Godau [1] presented an  $O(|A||B|\log^2(|A||B|))$  time algorithm. Later this bound was reduced to  $O(|A||B|\log(|A||B|))$  time [2].

We now define the discrete Fréchet distance following [6].

**Definition 2.1** *Given a polygonal chain (polyline) in 3D,  $P = \langle p_1, \dots, p_k \rangle$  of  $k$  vertices, a  **$m$ -walk** along  $P$  partitions the path into  $m$  disjoint non-empty subchains  $\{\mathcal{P}_i\}_{i=1..m}$  such that  $\mathcal{P}_i = \langle p_{k_{i-1}+1}, \dots, p_{k_i} \rangle$  and  $0 = k_0 < k_1 < \dots < k_m = k$ .*

*Given two 3D polylines  $A = \langle a_1, \dots, a_k \rangle$  and  $B = \langle b_1, \dots, b_l \rangle$ , a **paired walk** along  $A$  and  $B$  is a  $m$ -walk  $\{\mathcal{A}_i\}_{i=1..m}$  along  $A$  and a  $m$ -walk  $\{\mathcal{B}_i\}_{i=1..m}$  along  $B$  for some  $m$ , such that, for*

---

<sup>1</sup>This definition holds in any fixed dimensions.

$1 \leq i \leq m$ , either  $|\mathcal{A}_i| = 1$  or  $|\mathcal{B}_i| = 1$  (that is,  $\mathcal{A}_i$  or  $\mathcal{B}_i$  contains exactly one vertex). The **cost** of a paired walk  $W = \{(\mathcal{A}_i, \mathcal{B}_i)\}$  along two paths  $A$  and  $B$  is

$$d_F^W(A, B) = \max_i \max_{(a, b) \in \mathcal{A}_i \times \mathcal{B}_i} d(a, b).$$

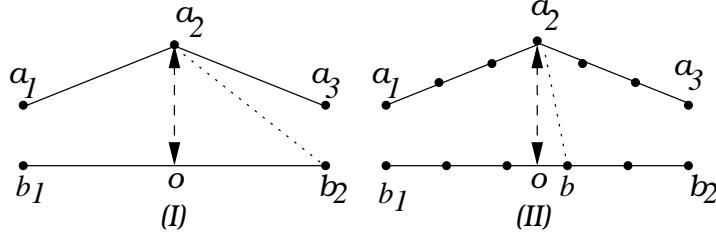
The **discrete Fréchet distance** between two polylines  $A$  and  $B$  is

$$d_F(A, B) = \min_W d_F^W(A, B).$$

The paired walk that achieves the discrete Fréchet distance between two paths  $A$  and  $B$  is also called the **Fréchet alignment** of  $A$  and  $B$ .

Consider the scenario in which the person walks (jumps) along  $A$  and the dog along  $B$ . Intuitively, the definition of the paired walk is based on three cases:

1.  $|\mathcal{B}_i| > |\mathcal{A}_i| = 1$ : the person stays and the dog moves (jumps) forward;
2.  $|\mathcal{A}_i| > |\mathcal{B}_i| = 1$ : the person moves (jumps) forward and the dog stays;
3.  $|\mathcal{A}_i| = |\mathcal{B}_i| = 1$ : both the person and the dog move (jump) forward.



**Fig. 1.** The relationship between discrete and continuous Fréchet distances.

Eiter and Mannila presented a simple dynamic programming algorithm to compute  $d_F(A, B)$  in  $O(|A||B|) = O(kl)$  time [6]. Recently, Jiang, *et al.* showed that the minimum discrete Fréchet distance between two chains in 2D,  $A$  and  $B$ , under translation can be computed in  $O(k^3l^3 \log(k+l))$  time, and under both translation and rotation it can be computed in  $O(k^4l^4 \log(k+l))$  time [14]. For 3D chains these bounds are  $O(k^4l^4 \log(k+l))$  and  $O(k^7l^7 \log(k+l))$  respectively [14]. They are significantly faster than the corresponding bounds for the continuous Fréchet distance (certainly due to a simpler distance structure), which are  $O((k+l)^{11} \log(k+l))$  and  $O((k+l)^{20} \log(k+l))$  respectively for 3D chains [22].

We comment that while the discrete Fréchet distance could be arbitrarily larger than the corresponding continuous Fréchet distance (e.g., in Fig. 1 (I), they are  $d(a_2, b_2)$  and  $d(a_2, o)$  respectively), by adding sample points on the polylines, one can easily obtain a close approximation of the continuous Fréchet distance using the discrete Fréchet distance (e.g., one can use  $d(a_2, b)$  in Fig. 1 (II)

to approximate  $d(a_2, o)$ ). This fact was pointed before in [6, 13] and is supported by the fact that the segments in protein backbones are mostly of similar lengths. Moreover, the discrete Fréchet distance is a more natural measure for matching the geometric shapes of biological sequences such as proteins. As we mentioned in the introduction, in such an application, continuous Fréchet does not make much sense to biologists.

In the remaining part of this paper, for the first time, we investigate the locally aligning a set of polygonal chains (proteins or protein backbones) in 3D, under the discrete Fréchet distance.

### 3 Protein Local Structure Alignment is Hard

Given a set of proteins modeled as simple 3D polygonal chains, the Protein Local Structure Alignment (PLSA) problem is defined as follows.

**Instance:** Given a set  $m$  of proteins  $P_1, P_2, \dots, P_m$  in 3D, each with length  $O(n)$ , and a real number  $D$ .

**Problem:** Does there exist a chain  $C$  of  $k$  vertices such that the vertices of  $C$  are from  $P_i$ 's, and  $C$  and a subsequence of  $P_i$  ( $1 \leq i \leq m$ ) has discrete Fréchet distance at most  $D$  (under translation and rotation)?

If no translation and rotation is allowed, we call the corresponding problem *static* PLSA. For the optimal version of the problem, we wish to maximize  $k$  when  $D$  is given. The (polynomial-time) approximation solution will also be referred to as approximating the optimal solution value  $k^*$  when it is hard to compute exactly. We will see that it is also hard to approximate  $k^*$  even for static PLSA. We first prove the following theorem.

**Theorem 3.1** *Given  $D = \delta$ , the static PLSA problem does not admit any approximation of factor  $n^{1-\epsilon}$  unless  $P=NP$ .*

*Proof.* It is easy to see that PLSA belongs to NP. We use a reduction from Independent Set to the Protein Local Structure Alignment Problem. Independent Set is a well known NP-complete problem which cannot be approximated within a factor of  $n^{1-\epsilon}$  [9]. The general idea is similar to that of the longest common subsequence problem for multiple sequences [15], but our details are much more involved due to the geometric properties of the problem.

Given a graph  $G = (V, E), V = \{v_1, v_2, \dots, v_N\}, E = \{e_1, e_2, \dots, e_M\}$ , we construct  $M + 1$  3D chains  $P_0, P_1, P_2, \dots, P_M$  as follows. (We assume that the vertices and edges in  $G$  are sorted by their corresponding indices.)

The overall reduction is as follows:  $\mathcal{P} = \{P_0, P_1, P_2, \dots, P_M\}$ , and

$$P_0 = \langle v'_1, v'_2, \dots, v'_n \rangle,$$

where  $v'_i = (i, i^2, 0)$  is a 3D point for  $i = 1, \dots, n$ .

For each  $e_r = (v_i, v_j)$  in  $G$ , we have a corresponding sequence (3D chain)

$$P_r = \langle v'_1, v'_2, \dots, v'_{i-1}, v'_{i+1}, \dots, v'_n, v''_1, v''_2, \dots, v''_{j-1}, v''_{j+1}, \dots, v''_n \rangle,$$

where  $v'_i = (i, i^2, 0)$  and  $v''_i = (i, i^2, \delta)$  are 3D points for  $i = 1, \dots, n$  and  $\delta$  is an arbitrarily small positive real number less than 0.1.

We claim that  $G$  has an independent set of size  $k$  if and only if there is a chain  $C$  of  $k$  vertices such that the discrete Fréchet distance between  $C$  and a subsequence of  $P_r$ ,  $S_r$ , is at most  $\delta$  (i.e.,  $d_F(C, S_r) \leq \delta$ ). The following claims are made with the detailed proofs left out.

**Claim A.**  $P_r$  is a simple polygonal chain in 3D.

**Claim B.**  $S_r$  is a simple polygonal chain in 3D with  $|S_r| = k$ .

If  $G$  has an independent set of size  $k$ , then the chain  $C$  can be constructed as follows. Let the independent set of  $G$  be ordered as  $I = \langle v_{i_1}, v_{i_2}, \dots, v_{i_k} \rangle$  with  $i_1 < i_2 < \dots < i_k$ . For  $r = 0, 1, \dots, M$ , we scan  $P_r$  in a greedy fashion to obtain the first  $v'_j$  or  $v''_j$  such that the first component of its coordinate is  $i_1$ . Repeat this process to obtain  $S_r$ . Then let any  $S_r$  be  $C$ . Obviously,  $C$  has  $k$  vertices and  $|S_r| = k$  for  $r = 0, 1, \dots, M$ .

If there is a chain  $C$  of  $k$  vertices such that the discrete Fréchet distance between  $C$  and a subsequence of  $P_r$ ,  $S_r$ , is at most  $\delta$  (i.e.,  $d_F(C, S_r) \leq \delta$ ), then we can see the following.

**Property (a)** Let  $P_r = \langle v'_1, v'_2, \dots, v'_{i-1}, v'_{i+1}, \dots, v'_n, v''_1, v''_2, \dots, v''_{j-1}, v''_{j+1}, \dots, v''_n \rangle$ , then  $d(v'_p, v''_q) > 3$  for all  $p \neq q$ .

**Property (b)** Let  $P_r = \langle v'_1, v'_2, \dots, v'_{i-1}, v'_{i+1}, \dots, v'_n, v''_1, v''_2, \dots, v''_{j-1}, v''_{j+1}, \dots, v''_n \rangle$ , then  $d(v'_p, v''_p) \leq \delta$  for all  $p \neq i, p \neq j$ .

**Property (c)** Let  $P_r = \langle u_1, u_2, \dots, u_{O(n)} \rangle$ , then  $|d(u_p, u_q) - d(u_{p'}, u_{q'})| >> \delta$  as long as the first components of the 4 coordinates of  $u_p, u_q, u_{p'}, u_{q'}$  are all different.

As  $\delta$  is very small, when  $d_F(C, S_r) \leq \delta$ , the vertices of  $C$  and  $S_r$  must be matched orderly in a one-to-one fashion. (In other words, the man walking on  $C$  and the dog walking on  $S_r$  must move/jump together at each vertex. Otherwise,  $d_F(C, S_r) > 3 >> \delta$ .) We now claim that the (ordered) vertices of  $C$  correspond to an independent set  $I$  of  $G$ ; moreover, if  $C = \langle C_1, C_2, \dots, C_k \rangle$  and  $C_p = (x_p, y_p, z_p)$ , then  $v_{x_p} \in I$ . Suppose that  $C_p = (x_p, y_p, z_p)$ ,  $C_q = (x_q, y_q, z_q)$  and  $v_{x_p}, v_{x_q} \in I$  but there is an edge  $e_t = (v_{x_p}, v_{x_q}) \in E$ . By our construction of  $P_t$  (from  $e_t$ ),  $v'_{x_p}$  and  $v''_{x_q}$  are not included in  $P_t$  and  $v'_{x_q}$  precedes  $v''_{x_p}$  in  $P_t$ . This is a contradiction.

To conclude the proof of this theorem, notice that the reduction take  $O(MN)$  time.  $\square$

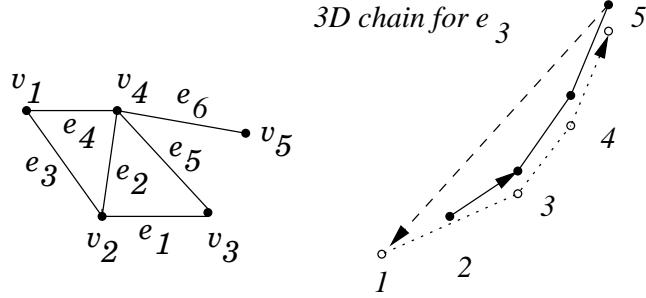
In the example shown in Figure 1, we have

$$P_1 = \langle v'_1, v'_3, v'_4, v'_5, v''_1, v''_2, v''_4, v''_5 \rangle,$$

$$P_2 = \langle v'_1, v'_3, v'_4, v'_5, v''_1, v''_2, v''_3, v''_5 \rangle,$$

$$P_3 = \langle v'_2, v'_3, v'_4, v'_5, v''_1, v''_3, v''_4, v''_5 \rangle,$$

$$P_4 = \langle v'_2, v'_3, v'_4, v'_5, v''_1, v''_2, v''_3, v''_5 \rangle,$$



**Figure 1.** Illustration of a simple graph for the reduction.

$$P_5 = \langle v'_1, v'_2, v'_4, v'_5, v''_1, v''_2, v''_3, v''_5 \rangle, \text{ and}$$

$$P_6 = \langle v'_1, v'_2, v'_3, v'_5, v''_1, v''_2, v''_3, v''_4 \rangle.$$

An example of  $P_3$  is shown in Figure 1 as well, in which case black nodes are on the  $Z = 0$  plane and white nodes are on the  $Z = \delta$  plane (apparently for the visualization reason, the XY-plane is slanted). The solid segments are on the  $Z = 0$  plane, the dotted segments are on the  $Z = \delta$  plane and the only dashed segment connects two points on different planes. Corresponding to the optimal independent set  $\{v_1, v_3, v_5\}$  in  $G$ , the optimal local alignment  $C = \langle v'_1, v'_3, v'_5 \rangle$  matches  $P_3$  at its subsequence  $S_3 = \langle v''_1, v''_3, v''_5 \rangle$ .

**Corollary 3.1** *Given  $D = \delta$  and when both translation and rotation are allowed, the (maximization version of) PLSA problem does not admit any approximation of factor  $n^{1-\epsilon}$  unless  $P=NP$ .*

*Proof.* Due to Property (a), (b) and (c), translation/rotation will not be able to generate another  $C'$  which is topologically different from  $C$ .  $\square$

Notice that in our proof all the adjacent vertices in  $C$  could be non-adjacent in  $P_i$ , for  $i = 0, 1, \dots, m$ . Biologically, this might be a problem as one residue alone sometimes cannot carry out any biological function. Define a  $c$ -substring or a  $c$ -subchain of  $P_i$  as a continuous subchain of  $P_i$  with at least  $c$  vertices. Unfortunately, even if we introduce this condition by forcing that  $C$  is composed of  $k$  ordered  $c$ -substrings of each  $P_i$ , for some constant  $c$ , the above proof can be modified to maintain a valid reduction from Independent Set. Call this corresponding problem Protein  $c$ -Local Structure Alignment (PcLSA), in which  $C$  must be composed of  $k$  ordered  $c$ -subchains of each  $P_i$ . We have the following corollary.

**Corollary 3.2** *The maximization version of PcLSA does not admit any approximation of factor  $n^{1-\epsilon}$  unless  $P=NP$ .*

## 4 Polynomial Time Solutions for PLSA When $m$ is Small

In this section, we present a polynomial time solution for the PLSA problem when  $m$  is a constant. We first show a dynamic programming solution for the static PLSA and then we show how to use

that as a subroutine for the general PLSA problem, when  $m$  is small.

#### 4.1 A Dynamic Programming Solution for the Static PLSA When $m$ is Small

In this subsection, we present a dynamic programming solution for the static PLSA problem when  $m$  is small. Such a solution can be used as a subroutine for the general PLSA problem. We first consider the case when  $m = 2$ . Besides  $C$ , we try to maximize the length of the aligned subsequences in  $P_1 = A$  and  $P_2 = B$  with  $|A| = n_1, |B| = n_2$ . For the ease of description, we only show how to obtain these lengths which are stored in  $D[-, -, -, -]$  and  $M[-, -, -, -]$  respectively. It is easy to reconstruct  $C$  from these arrays.

Let  $A[i_1, i_2]$  be a subchain of  $A$  starting from the index  $i_1$  and ending at the index  $i_2$ . Let  $B[j_1, j_2]$  be a subchain of  $B$  starting from the index  $j_1$  and ending at the index  $j_2$ .  $D[i_1, i_2, j_1, j_2]$  stores the length of the aligned subsequences of  $A[i_1, i_2]$  as a consequence of the alignment of  $C$  and  $A[i_1, i_2]$ , and  $C$  and  $B[j_1, j_2]$ .  $M[i_1, i_2, j_1, j_2]$  is defined symmetrically.

Intuitively  $D[-, -, -, -]$  stores the length of aligned subsequences from chain  $A$  (dog's route) and  $M[-, -, -, -]$  stores the length of aligned subsequences from chain  $B$  (man's route). Define  $T_F(i_1, i_2, j_1, j_2)$  as the sum of aligned subsequences in both  $A[i_1, i_2]$  and  $B[j_1, j_2]$ . Writing  $A[i]$  as  $a_i$  and  $B[j]$  as  $b_j$ , we have the dynamic programming solution as follows.

$$T_F(i_1, i_2, j_1, j_2) = D(i_1, i_2, j_1, j_2) + M(i_1, i_2, j_1, j_2),$$

where

$$D(i_1, i_2, j_1, j_2) = \max \begin{cases} \max_{i_1 \leq k_1 < i_2} \{D(i_1, k_1, j_1, j_2) + 1\} & \text{if } d(a_{i_2}, b_{j_2}) \leq \delta, \text{ dog moves} \\ \max_{i_1 \leq k_1 < i_2, j_1 \leq k_2 < j_2} \{D(i_1, k_1, j_1, k_2) + 1\} & \text{if } d(a_{i_2}, b_{j_2}) \leq \delta, \text{ both move} \\ \max_{j_1 \leq k_2 < j_2} \{D(i_1, i_2, j_1, k_2)\} & \text{if } d(a_{i_2}, b_{j_2}) \leq \delta, \text{ dog stays} \end{cases} \quad (1)$$

and

$$M(i_1, i_2, j_1, j_2) = \max \begin{cases} \max_{i_1 \leq k_1 < i_2} \{M(i_1, k_1, j_1, j_2)\} & \text{if } d(a_{i_2}, b_{j_2}) \leq \delta, \text{ man stays} \\ \max_{i_1 \leq k_1 < i_2, j_1 \leq k_2 < j_2} \{M(i_1, k_1, j_1, k_2) + 1\} & \text{if } d(a_{i_2}, b_{j_2}) \leq \delta, \text{ both move} \\ \max_{j_1 \leq k_2 < j_2} \{M(i_1, i_2, j_1, k_2) + 1\} & \text{if } d(a_{i_2}, b_{j_2}) \leq \delta, \text{ man moves} \end{cases} \quad (2)$$

The boundary cases are handled as follows.

$$D(i_1, i_1, j_1, j_1) = M(i_1, i_1, j_1, j_1) = \begin{cases} 1 & \text{if } d(a_{i_1}, b_{j_1}) \leq \delta, \\ 0 & \text{if } d(a_{i_1}, b_{j_1}) > \delta. \end{cases} \quad (3)$$

The final solution value is stored in  $T_F[1, n_1, 1, n_2]$ . We have the following theorem.

**Theorem 4.1** *When  $m = 2$ , the static PLSA problem can be solved in  $O(n^4)$  time and space.*

It is easy to generalize this algorithm to the more general case when  $m$  is some constant. We thus have the following corollary.

**Corollary 4.1** *When  $m$  is a constant, the static PLSA problem can be solved in  $O(m^3n^{2m})$  time and  $O(mn^{2m})$  space.*

## 4.2 A Polynomial Time Solution for PLSA When $m$ is Small

Apparently, for any solution for PLSA we should allow translation and rotation. When  $m = 2$  and when both translation and rotation are allowed, we can use a method similar to that in [14] to compute the optimal local alignment with fixed  $\delta$ . The idea is as follows. Without loss of generality, we assume that  $A$  is static and we translate/rotate  $B$  and let  $\tau(B)$  be the copy of  $B$  after some translation/rotation. Let  $|A| = n_1, |B| = n_2$  and let  $f$  be the degree of freedom for moving  $B$ . As we are in 3D and both translation and rotation are allowed, we have  $f = 6$ . We can enumerate all possible configurations for  $A$  and  $\tau(B)$  to realize a discrete Fréchet distance of  $\delta$ . There are  $O((n_1 n_2)^f) = O(n^{12})$  number of such configurations, following an argument similar to [22, 14]. Then for each configuration, we can use the above Theorem 4.1 to obtain the optimal local alignment for each configuration and finally we simply return the overall optimal solution.

**Corollary 4.2** *When  $m = 2$  and when both translation and rotation are allowed, the PLSA problem can be solved in  $O(n^{16})$  time and  $O(n^4)$  space.*

We comment that when  $m$  is larger, but still a constant, the above idea can be carried over so that we will still be able to solve PLSA in polynomial time. It follows from [22, 14] that we have  $O(n^{mf}) = O(n^{6m})$  number of configurations between the  $m$  chains. Then we can again use Corollary 4.1 to obtain the optimal local alignment for each configuration. The overall complexity would be  $O(n^{6m} \times m^3 n^{2m}) = O(m^3 n^{8m})$  time and  $O(mn^{2m})$  space. Certainly, such an algorithm is only meaningful in theory.

**Corollary 4.3** *When  $m$  is a constant and when both translation and rotation are allowed, the PLSA problem can be solved in  $O(m^3 n^{8m})$  time and  $O(mn^{2m})$  space.*

## 5 Concluding Remarks

In this paper, for the first time, we study the complexity/algorithms aspects of the famous protein local structure alignment problem under the discrete Fréchet distance. We show that the general problem is NP-complete; in fact, it is even NP-hard to approximate within a factor of  $n^{1-\epsilon}$ . On the other hand, when a constant number of proteins are given then the problem can be solved in

polynomial time. It would be interesting to see the empirical comparisons of protein local structure alignment under the discrete Fréchet distance with the existing methods. Another open problem, obviously, is whether it is possible to improve the running time of the dynamic programming algorithms in Section 4.

## References

- [1] H. Alt and M. Godau. Measuring the resemblance of polygonal curves. In *Proceedings of the 8th Annual Symposium on Computational Geometry (SoCG'92)*, pages 102–109, 1992.
- [2] H. Alt and M. Godau. Computing the Fréchet distance between two polygonal curves. *Intl. J. Computational Geometry and Applications*, **5**:75–91, 1995.
- [3] H. Alt, C. Knauer and C. Wenk. Matching polygonal curves with respect to the Fréchet distance. In *Proceedings of the 18th Annual Symposium on Theoretical Aspects of Computer Science (STACS'01)*, pages 63–74, 2001.
- [4] K. Buchin, M. Buchin and C. Wenk. Computing the Fréchet distance between simple polygons in polynomial time. In *Proceedings of the 22nd Annual Symposium on Computational Geometry (SoCG'06)*, pages 80–87, 2006.
- [5] L. Conte, B. Ailey, T. Hubbard, S. Brenner, A. Murzin and C. Chothia. SCOP: a structural classification of protein database. *Nucleic Acids Res.*, **28**:257-259, 2000.
- [6] T. Eiter and H. Mannila. Computing discrete Fréchet distance. *Tech. Report CD-TR 94/64, Information Systems Department, Technical University of Vienna*, 1994.
- [7] M. Fréchet. Sur quelques points du calcul fonctionnel. *Rendiconti del Circolo Mathematico di Palermo*, **22**:1-74, 1906.
- [8] M. Godau. On the complexity of measuring the similarity between geometric objects in higher dimensions. *PhD thesis, Freie Universitaet Berlin*, 1998.
- [9] J. Hästad. Clique is hard to approximate within  $n^{1-\epsilon}$ . *Acta Mathematica*, **182**:105-142, 1999.
- [10] L. Holm and J. Park. DALI Lite workbench for protein structure comparison. *Bioinformatics*, **16**:566-567, 2000.
- [11] L. Holm and C. Sander. Protein structure comparison by alignment of distance matrices. *J. Mol. Biol.*, **233**:123-138, 1993.
- [12] P. Hui and M. Shaefer. Paired pointset traversal. In *Proceedings of the 15th Annual Symposium on Algorithms and Computation (ISAAC'04)*, pages 534-544, 2004.

- [13] P. Indyk. Approximate nearest neighbor algorithms for Fréchet distance via product metrics. In *Proceedings of the 18th Annual Symposium on Computational Geometry (SoCG'02)*, pages 102–106, 2002.
- [14] M. Jiang, Y. Xu and B. Zhu. Protein structure-structure alignment with discrete Fréchet distance. In *Proceedings of the 5th Asia-Pacific Bioinformatics Conf. (APBC'07)*, pages 131–141, 2007. (Revised version to appear in J. of Bioinformatics and Computational Biology.)
- [15] T. Jiang and M. Li. On the approximation of shortest common supersequences and longest common subsequences. *SIAM J. Comput.*, **24**(5):1122–1139, 1995.
- [16] X. Miao, P. Waddell and H. Valafar. TALI: Local alignment of protein structures using backbone torsion angles. *J. of Bioinformatics and Computational Biology.*, to appear, 2008.
- [17] C. Orengo, A. Michie, S. Jones, D. Jones, M. Swindles and J. Thornton. CATH—a hierachic classification of protein domain structures. *Structure*, **5**:1093–1108, 1997.
- [18] A. Ortiz, C. Strauss and O. Olmea. MMAMOTH (matching molecular models obtained from theory): an automated method for model comparison. *Protein Science*, **11**:2606–2621, 2002.
- [19] J. Qian, S. Li, D. Bu, M. Li and J. Xu. Finding compact structural motifs. In *Proceedings of the 18th Annual Symposium on Combinatorial Pattern Matching (CPM'07)*, pages 142–149, 2007.
- [20] I. Shindyalov and P. Bourne. Protein structure alignment by incremental combinatorial extension (CE) of the optimal path. *Protein Engineering*, **11**:739–747, 1998.
- [21] W. Taylor and C. Orengo. Protein structure alignment. *J. Mol. Biol.*, **208**:1–22, 1989.
- [22] C. Wenk. Shape Matching in Higher Dimensions. *PhD thesis, Freie Universitaet Berlin*, 2002.